Clinical features and severity grading of anaphylaxis

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Background: Existing grading systems for acute systemic hypersensitivity reactions vary considerably, have a number of deficiencies, and lack a consistent definition of anaphylaxis.
Objective: The aims of this study were to develop a simple grading system and definition of anaphylaxis and to identify predictors of reaction severity.
Methods: Case records from 1149 systemic hypersensitivity reactions presenting to an emergency department were analyzed retrospectively. Logistic regression analyses of the associations between individual reaction features and hypotension and hypoxia were used to construct a grading system. Epinephrine use, etiology, age, sex, comorbidities, and concurrent medications were then assessed for their association with reaction grade.
Results: Confusion, collapse, unconsciousness, and incontinence were strongly associated with hypotension and hypoxia and were used to define severe reactions. Diaphoresis, vomiting, presyncope, dyspnea, stridor, wheeze, chest/throat tightness, nausea, vomiting, and abdominal pain had weaker, albeit significant, associations and were used to define moderate reactions. Reactions limited to the skin (urticaria, erythema, and angioedema) were defined as mild. These grades correlated well with epinephrine usage. Older age, insect venom, and iatrogenic causes were independent predictors of severity. Preexisting lung disease was associated with an increased risk of hypoxia.
Conclusion: This simple grading system has potential value for defining reaction severity in clinical practice and research settings. The moderate and severe grades provide a workable definition of anaphylaxis. Age, reaction precipitant, and preexisting lung disease appear to be the major determinants of reaction severity. (J Allergy Clin Immunol 2004;114:371-6.)

Key words: *Anaphylaxis, immediate hypersensitivity, etiology, classification, severity*

Abbreviations used
ACE: angiotensin-converting enzyme
ED: Emergency department
LOC: Loss of consciousness
SpO_2: Oxygen saturation measured by pulse oximetry
TIA: Transient ischemic attack

It has been reported that systemic hypersensitivity syndromes, ranging from mild urticaria to major cardiovascular compromise, account for about 1 in every 200 adult emergency department (ED) presentations.[1] However, definitions of acute allergic syndromes and anaphylaxis vary considerably, leading to difficulties designing and interpreting clinical studies.[2] Anaphylaxis often occurs in poorly monitored environments outside a hospital and may resolve spontaneously or with treatment prior to ED arrival. Therefore, classification systems need to be relatively simple and easy to apply retrospectively.

Although a number of severity grading systems have been described, they appear to be based on clinical reasoning rather than statistical analysis of the relationships between individual reaction features. Approaches range from simple descriptions of key symptoms,[3,4] to complex "2 or more" rules,[5,6] sums of scores,[7] or physiologic parameters that may not be available when assessing a reaction that has occurred outside a monitored environment.[1] Some authors consider cardiovascular compromise to be more severe than respiratory compromise,[4,8,9] with 1 system focusing almost entirely on the severity of cardiovascular collapse.[10,11] However, weighting cardiovascular compromise above respiratory compromise is not supported by observations that death may be due mainly to respiratory compromise, cardiovascular compromise, or both.[12]

The main aim of this study was to develop a simple clinical grading system and definition for anaphylaxis, based on the premise that unequivocal compromise of either the cardiovascular system or the respiratory system defines a severe reaction. A secondary aim was to identify predictors of reaction severity.

METHODS

Study design and setting

This was a retrospective analysis of the presenting clinical features and treatment of acute generalized hypersensitivity reactions. A computerized information system with details of 315,110 presentations to the Royal Hobart Hospital ED from October 1990 to December 1999 inclusive was used to identify cases. The Royal Hobart Hospital is a mixed (adult and pediatric) tertiary referral hospital where *Myrmecia* ant and honeybee stings are common causes of anaphylaxis.[13]

Medical records were retrieved for those presentations given a diagnosis of anaphylaxis, insect sting, or with triage descriptions containing the text strings anaph*, allerg*, or react*. The hospital inpatient master index was also queried to identify cases miscoded in the ED database. Cases were included if the medical notes recorded a diagnosis of a hypersensitivity or allergic reaction and the clinical

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presentation included any generalized skin, gastrointestinal, respiratory, cardiovascular, or neurological manifestations. Nonurticarial skin reactions and isolated angioedema secondary to angiotensin-converting enzyme (ACE) inhibitors without other features of systemic mediator release were not included if the medical record indicated these diagnoses. Reactions to treatment given in the ED for other conditions were not included, as these events were not recorded in the computer databases.

Data elements were recorded on a structured datasheet or entered directly into a customized Microsoft Access database by 2 trained research staff (a medical student and a research nurse). Approval for the study was obtained from the Royal Hobart Hospital Ethics Committee.

Measurements

For each case the following details were obtained from ambulance sheets, referral letters, and case notes: age, sex, regular cardioactive medications (antihypertensives including β-blockers and ACE inhibitors), common comorbidities (asthma, chronic airflow limitation, hypertension, ischemic heart disease, heart failure, previous stroke, or transient ischemic attack [TIA]), individual reaction features (symptoms and signs), likely reaction cause (if identified), and epinephrine administration. Histories of "hay fever" and "atopy" were not recorded, as the relevant diagnostic criteria were unlikely to have been applied.

Data analysis

To develop the grading system, documented hypotension (systolic < 90 mm Hg in adults, lower in children according to age), cyanosis, or pulse oximetry saturations (SpO_2) ≤ 92% were used as primary indicators of physiologic severity. Individual reaction features associated with these markers were identified using the Fisher Exact Test (significance level $<.05$). Backward stepwise logistic regression analysis was then performed to identify a minimum set of predictors. These results were used to construct the grading system.

The relationship between the resulting severity grades and epinephrine administration was assessed by Spearman rank correlation. Etiology (grouped as venom, food, iatrogenic-oral, iatrogenic-parenteral, topical or inhaled, and unidentified cause), demographic features (age, sex), comorbidities, and regular medications were assessed for their association with reaction severity by multinomial logistic regression analysis. Statistical analyses were performed with SPPS software version 11 and Analyse-it version 1.61 for Microsoft Excel.

RESULTS

Dataset characteristics

Two thousand thirty-two records identified by the database search were reviewed, of which 1149 satisfied our inclusion criteria. Five hundred forty-four (47%) were male. Ages ranged from 0 to 96 years, with a median of 29 years (17 aged < 1 year, 237 aged 1 to 14 years, 421 aged 14 to 35 years, and 474 aged >35). In 118 (10%) a history of 1 or more cardiovascular diseases were recorded (hypertension, 83; ischemic heart disease, 43; heart failure, 7; stroke or TIA, 9) and in 212 (18%) a history of airways disease was recorded (asthma, 193; chronic airflow limitation, 19). Seventy-two (6.0%) were prescribed β-blockers and/or ACE inhibitors (β-blockers only 15, ACE inhibitors only 51, both 6). A breakdown of identified reaction causes is presented in Table I. The incidences of individual reaction features and a univariate analysis of each feature's relationship with the occurrence of hypotension and hypoxia are presented in Table II. Three hundred seventy-two reactions (32%) were treated with epinephrine; 169 received epinephrine prehospital only, 156 in hospital only, and 47 both pre- and in hospital. Five people received cardiopulmonary resuscitation); 3 died later in hospital (1 each caused by polygeline infusion, oral penicillin, and *Myrmecia* ant sting), and 2 were successfully resuscitated (one after a bee sting, another after the administration of sublingual glyceryl trinitrate for chest and throat tightness, breathlessness, and wheeze that occurred after taking oral amoxicillin).

Grading system

The minimum sets of predictors of hypotension and hypoxia identified by stepwise logistic regression analysis are listed in Tables III and IV, respectively. Those features showing the highest correlation with either hypotension or hypoxemia were also clinical signs of neurologic compromise well known to result from hypotension and hypoxia. These features (incontinence, collapse, and confusion) along with measured hypotension or hypoxia were therefore used to define severe reactions. Features significantly but less closely associated with hypotension and hypoxia were either characteristic of processes that can lead to hypotension or hypoxia (dyspnea, stridor, wheeze) or nonspecific features of severe illness potentially caused by tissue hypoperfusion and/or anaphylactic mediators (nausea, vomiting, dizziness [presyncope], diaphoresis, chest or throat tightness, abdominal pain). These were used to define moderately severe reactions. None of the common objective skin features (urticaria, erythema, periorbital edema, angioedema) correlated with hypoxia or hypotension. These were therefore used to define mild reactions.

Using this system, only 1125 cases could be classified initially (mild, 545; moderate, 441; severe, 139). Of the remaining 24, 10 presented with generalized itch or malaise without any other recorded reaction features. Only one had been treated by epinephrine (prophylactically by the patient). Because of doubts as to whether these represented hypersensitivity reactions, they were not included in subsequent analyses. Case notes for the remaining 14 recorded only chest/throat tightness (12) or abdominal pain (2). Five were treated with epinephrine, suggesting significant distress or a failure to document other features of anaphylaxis. Logistic regression analysis indicated that chest/throat tightness and abdominal pain were associated with other "moderate" features, so they were added as criteria for this grade. The final classification system is presented in Table V.

Within the mild grade, 63/545 (12%) were recorded as having angioedema without any other objective skin features. In the moderate and severe grades, respectively, 99/455 (22%) and 23/139 (17%) did not have any objective skin features documented in the medical record.

As demonstrated in Table VI, a significant correlation was found between reaction grade and the frequency of epinephrine use. Total epinephrine dose was also related

to reaction grade; a greater proportion of people with higher-grade reactions received greater than the median dose of epinephrine. Within the moderate and severe grades, epinephrine administration did not differ significantly between those recorded to have skin features and those without. Within the mild grade, epinephrine administration rates were significantly higher in those with angioedema (24% versus 9.5%, $P < .0001$), although the total doses did not differ significantly. This suggested the potential to further subdivide mild reactions into those with and without angioedema.

Factors associated with reaction severity

Univariate analyses suggested that reaction severity was influenced by age, ACE inhibitor and β-blocker medication, known lung disease, and etiology. However, multinomial logistic regression analysis found that the only independent associations with the severe reaction grade were insect venom (odds ratio 2.7, 95% CI 1.8-4.2), iatrogenic causes (odds ratio 2.3; 95% CI 1.4-3.8), and older age (median ages 26, 29, and 44 years for mild, moderate, and severe reactions, respectively; $P < .0001$). Within each etiological subgroup, the association between age and severity was significant except for in reactions due to food (median ages 20.5, 23, and 28 for mild, moderate, and severe reactions, respectively; $P = .2262$). A breakdown of reaction grade by etiology is presented in Figure 1, which also indicates a predominance of unknown reaction causes in the mild category.

Although preexisting lung disease was not significantly associated with the severe reaction grade, it was significantly associated with hypoxia. This effect was independent of etiology, age, ACE inhibitor and β-blocker medication, and other comorbidities (multinomial logistic regression analysis: odds ratio 2.3; 95% CI 1.2-4.5; $P = .012$). After controlling for age, ACE inhibitor and β-blocker medications were not significantly associated with the occurrence of documented hypotension, collapse, or hypoxia.

TABLE I. ED assessment of likely etiology of 1149 cases initially diagnosed as generalized hypersensitivity reactions

Venomous stings and bites, n = 342 (30%)	
Ant (*Myrmecia spp*)*	165
Bee (*Apis mellifera*)	71
Yellow jacket (*Vespula germanica*)	16
Others†	11
Unidentified sting or bite	79
Iatrogenic, n = 250 (22%)	
Antibiotic‡	145
Nonsteroidal anti-inflammatory	32
Narcotic	11
Radiologic contrast	7
ACE inhibitor§	4
Vaccine†	4
Others or uncertain	47
Food, n = 205 (18%)	
Sea food	47
Nut	46
Egg	14
Monosodium glutamate†	7
Kiwi fruit	4
Others or uncertain	87
Other, n = 61 (5%)	
Topical exposure or inhaled†	57
Exercise-induced	4
Unidentified, n = 291 (25%)	291

ACE, angiotensin-converting enzyme.
**Myrmecia pilosula* ("jack jumper ant") in 135, *Myrmecia forficata* ("inchman ant") in 10. Ants were seen but no clearly identified in 20 cases.
†Causes that did not precipitate any severe reactions (hypotension or hypoxia) in this series.
‡The most commonly implicated antibiotics were penicillins (73), cephalosporins (27), and cotrimoxazole (18) and were administered orally in 139 (96%) of cases.
§Simple angioedema (no other skin or systemic features) due to ACE inhibitor were not included; the reactions here included other features of anaphylaxis.

DISCUSSION

This study found that confusion, collapse, unconsciousness, incontinence, diaphoresis, vomiting, presyncope, dyspnea, stridor, wheeze, nausea, and vomiting were associated with documented hypotension and hypoxia. A simple grading system was then devised with the above features separated into moderate and severe grades according to degree of association and pathophysiologic considerations. The resulting grades correlated well with epinephrine usage. Older age, insect venom, and iatrogenic causes were independent predictors of severity, and preexisting lung disease was associated with an increased risk of hypoxia. Unknown reaction causes were more frequent in the mild group.

Methodological limitations inherent in the retrospective design included a reliance on accurate medical records, exclusion of iatrogenic causes occurring after hospital admission, and the fact that all reactions (and treatment with epinephrine in 19%) commenced prior to arrival in hospital. Therefore, many reaction features are likely to have gone undocumented. In particular, hypotension and hypoxia would not have been detected in a significant number of cases. The absence of documented skin involvement in 17% to 22% of moderate to severe reactions may be due to resolution with prior epinephrine treatment or the fact that skin involvement can be easily missed when present—when carefully observed, some degree of skin involvement (although often subtle, such as mild erythema) appears to be nearly universal.[1,14] Nevertheless, it is clear that a number of symptoms are clearly linked with hypotension and hypoxia and can therefore be used as indicators of reaction severity when analyzing cases retrospectively. Another limitation to this study is that etiology was based on ED assessments rather than allergist review with confirmatory skin testing and specific immunoglobulin E analysis where appropriate. For this reason, analysis of presumed etiology has been based on broad subgroups rather than on specific causative agents.

TABLE II. Individual clinical reaction features associated with documented hypotension or hypoxia

Clinical feature	N	(%)	Number that also had documented: Hypotension	*P*	Cyanosis/$SpO_2 \leq 92\%$	*P*
General						
Anxiety	103	(9%)	7	.832	3	1.000
Paresthesia	34	(3%)	3	.471	0	.634
Malaise	43	(3%)	4	.345	2	.673
Weakness	14	(1%)	5	.001	0	1.000
Feeling of impending doom	7	(0.6%)	3	.007	0	1.000
Skin						
Generalized itch	555	(48%)	34	.809	19	.643
Periorbital edema	232	(20%)	17	.546	6	.437
Generalized urticaria/erythema	835	(73%)	59	.106	30	.728
Angioedema	446	(39%)	26	.620	19	.525
Gastrointestinal						
Chest or throat tightness	275	(24%)	21	.322	13	.361
Chest pain	16	(1%)	2	.270	1	.458
Abdominal pain	70	(6%)	7	.202	2	1.000
Nausea	154	(13%)	27	<.001	6	.822
Vomiting	112	(10%)	25	<.001	9	.030
Diarrhea	32	(3%)	6	.013	1	1.000
Incontinence	5	(0.4%)	4	<.001	0	1.000
Respiratory						
Difficulty swallowing	46	(4%)	4	.529	2	.688
Coryzal symptoms	23	(2%)	1	1.000	0	1.000
Difficulty speaking	22	(2%)	3	.159	2	.197
Hoarse voice	25	(2%)	1	1.000	0	1.000
Stridor	33	(3%)	3	.461	6	.001
Cough	25	(2%)	0	.399	1	.618
Wheeze	148	(13%)	15	.048	16	<.001
Dyspnea	338	(29%)	37	<.001	27	<.001
Cyanosis or $SpO_2 \leq 92\%$	43	(4%)	9	.001	43	—
Cardiovascular and neurologic						
Dizziness (pre syncope)	115	(10%)	28	<.001	2	.306
Visual disturbance	19	(2%)	6	.001	1	.518
Diaphoresis	47	(4%)	18	<.001	4	.094
Pallor	12	(1%)	4	.005	2	.071
Headache	29	(3%)	2	.706	1	1.000
Confusion	5	(0.4%)	3	.002	2	.013
Collapse (inc LOC)*	59	(5%)	25	<.001	6	.019
LOC	17	(2%)	8	<.001	2	.13
Hypotension	73	(6%)	73	-	9	.001

LOC, Loss of consciousness.

A major difference between the results here and other published approaches is the importance of gastrointestinal features. These may represent direct mediator effects or poor perfusion at a tissue level prior to the onset of hypotension. Various modifications of the widely used Mueller system have considered gastrointestinal manifestations to be less serious than those affecting the respiratory system, and equivalent in importance to angioedema.[5,6,8,9,13,15,16] One of these studies found modified Mueller grades to correlate well with epinephrine administration in the setting of insect venom allergy.[13] Other systems do not assign any importance to gastrointestinal features.[3,4] Although some authors have recognized the importance of gastrointestinal manifestations,[1,10,17] this study is the first to clearly demonstrate the important association between such features and hypotensive anaphylaxis.

The finding that age is a major determinant of reaction severity is consistent with previous prospective sting allergy studies[8,13] and a recent large mortality study that found insect venom and iatrogenic anaphylactic deaths to have median ages of 54-67 years.[12] The data here indicating an insignificant effect of increasing age on reaction severity in food anaphylaxis are also consistent with the fact that food anaphylaxis deaths have a younger median age of 22-24 years.[12] Alternatively, the younger age of food anaphylaxis deaths may simply represent the earlier age at which exposure to allergenic foodstuffs begins, and the prominence of venom and iatrogenic causes in severe reactions in this study may be due to the

TABLE III. Logistic regression analysis: minimum set of predictors for documented hypotension, ranked by odds ratio

Clinical feature	Documented hypotension Odds ratio (95% CI)	P
Incontinence	13 (1.2-143)	.033
Collapse (includes LOC)	6.3 (3.1-13)	<.001
Diaphoresis	4.0 (1.9-8.5)	<.001
Cyanosis or SpO_2 < 92%	3.4 (1.3-8.4)	.010
Vomiting	2.9 (1.5-5.6)	.002
Dizziness (presyncope)	2.7 (1.4-5.3)	.003
Dyspnea	2.1 (1.2-3.7)	.008
Nausea	2.2 (1.1-4.2)	.018

LOC, Loss of consciousness.

TABLE IV. Logistic regression analysis: minimum set of predictors for cyanosis or $SpO_2 \leq 92\%$, ranked by odds ratio

Clinical feature	Documented cyanosis or $SpO_2 \leq 92\%$ Odds ratio (95% CI)	P
Confusion	9.9 (1.3-77)	.028
Stridor	3.8 (1.4-10)	.008
Dyspnea	2.9 (1.4-5.7)	.003
Hypotension	2.9 (1.3-6.8)	.013
Wheeze	2.2 (1.1-4.6)	.028

increasing prevalence of insect venom allergy with older age[13] and a grading system bias that favors hypotensive reaction features. This bias may have arisen if hypoxia due to bronchospasm, a common manifestation of lethal and near-lethal food anaphylaxis,[12,18] went unrecognized or was poorly documented.

ACE inhibitors,[19,20] β-blockers,[21-23] cardiovascular comorbidities,[24] and respiratory comorbidities[18] have been implicated in severe reactions and death. Although this study supports the importance of respiratory comorbidity in predisposing to hypoxia, presumably because of reduced respiratory physiological reserve and/or a predisposition to bronchospasm, it did not find that cardiovascular comorbidities and medications were independent predictors of any severe reaction feature. Although such an effect cannot be excluded by a retrospective study where such conditions may have gone unrecognized, the results indicate that older age is a more important predictor of reaction severity. Comorbidities and medications might be important in determining lethality rather than initial reaction severity.

Any study of acute allergic reactions is limited by the lack of a diagnostic gold standard or widely accepted definition of anaphylaxis. One recent ED study defined reactions limited to the skin (including angioedema) as "acute allergic reactions," reserving the term "anaphylaxis" for reactions with additional gastrointestinal, respiratory, cardiovascular, or neurological features.[1]

TABLE V. Grading system for generalized hypersensitivity reactions

Grade	Defined by
1—Mild (skin and subcutaneous tissues only)*	Generalized erythema, urticaria, periorbital edema, or angioedema
2—Moderate (features suggesting respiratory, cardiovascular, or gastrointestinal involvement)	Dyspnea, stridor, wheeze, nausea, vomiting, dizziness (presyncope), diaphoresis, chest or throat tightness, or abdominal pain
3—Severe (hypoxia, hypotension, or neurologic compromise)	Cyanosis or $SpO_2 \leq 92\%$ at any stage, hypotension (SBP < 90 mm Hg in adults), confusion, collapse, LOC, or incontinence

SBP, Systolic blood pressure; *LOC*, loss of consciousness.
*Mild reactions can be further subclassified into those with and without angioedema (see text).

TABLE VI. Reaction grade versus treatment with epinephrine

		Epinephrine use		
		Total epinephrine dose in adult patients (mg)†		
Grade	N (%)*	Mean dose	Median dose	Proportion receiving more than the median dose
Mild (n = 545)	83 (15%)	0.46	0.45	0.19
Moderate (n = 455)	194 (42%)	0.54	0.50	0.25
Severe (n = 139)	94 (68%)	0.97	0.50	0.37

*Spearman correlation coefficient 0.387, $P < .0001$.
†Spearman correlation coefficient 0.13, $P = .0307$; the analysis of total dose was restricted to adults (age > 14) because of the confounding effect of age on adrenaline dose.

Another ED study used a similar definition of anaphylaxis, except that angioedema of the lips or tongue was considered a respiratory feature and thus diagnostic of anaphylaxis.[17] A position statement by the European Academy of Allergology and Clinical Immunology defines anaphylaxis as "severe, life-threatening, multiple-organ hypersensitivity, often dominated by severe asthma and hypotension" but also states "these do not have to be present for a reaction to be classified as anaphylaxis."[25]

Consistent with the above approaches, the results presented here support a definition of anaphylaxis that includes any of the features listed in the moderate and severe grades, as these are associated with hypoxia and/or hypotension. Clinicians should be aware that a history of any of these symptoms suggests the possibility of hypoxia or hypotension when direct observation has not been possible. This study did not find angioedema to be associated with hypoxia or hypotension. The relative abundance of unknown etiologies in the mild (skin only)

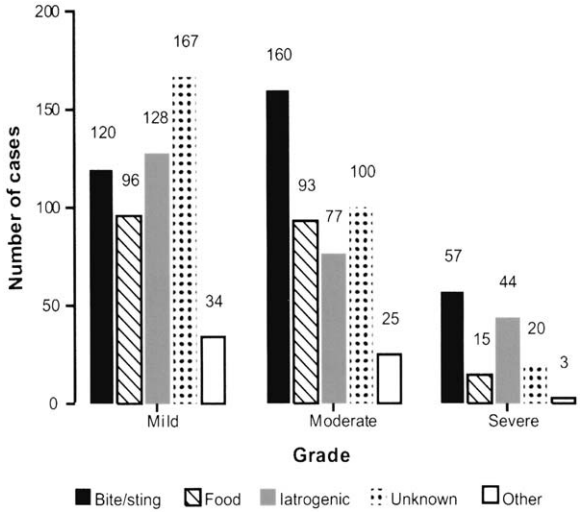

FIG 1. Reaction grade according to etiology.

grade is similar to previous findings[1] and suggests that many such cases may be due to causes (including nonallergic) that are not associated with anaphylaxis.

As discussed above, when carefully observed virtually all episodes of anaphylaxis appear to have some degree of skin involvement, although this may consist of only mild erythema and can be easily missed or go undocumented as is likely to have been the case in this study. With this in mind, the following clinical definition of anaphylaxis is proposed: "Multiple-organ hypersensitivity characterized by the presence of significant gastrointestinal, respiratory, or cardiovascular involvement (nausea, vomiting, abdominal pain, throat or chest tightness, breathlessness, wheeze, stridor, hypotension, hypoxia, confusion, collapse, loss of consciousness, or incontinence) in addition to skin features (erythema, urticaria, or angioedema). Skin features may be transient, subtle, and therefore easily missed, in which case anaphylaxis may still be diagnosed if there is an otherwise typical presentation, especially where this follows exposure to a known precipitant."

Although reaction severity in an individual may fluctuate over time, studies of insect venom allergy have suggested that prior maximal reaction severity may be used to predict subsequent reaction severity (subsequent reactions being of similar or lesser severity) and thus select people who are most likely to benefit from immunotherapy and to carry self-administered epinephrine.[8,9,13] Severity grading and analysis of the baseline characteristics that determine reaction severity are also important components of anaphylaxis research. A prospective evaluation of this system in terms of ease and accuracy of application, and as a guide for subsequent therapy, is therefore warranted.

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